NEUROEPIDEMIOLOGY

Epidemiology of peripheral neuropathy

C N Martyn, R A C Hughes

Peripheral neuropathy occurs as a component of several common and many rare diseases. It is heterogenous in aetiology, diverse in pathology, and varied in severity. The term peripheral neuropathy includes symmetric polyneuropathy, single and multiple mononeuropathy, and radiculopathy. Further classification depends on a mixture of phenomenological, pathological, and genetic or other aetiological features. All of these things cause problems for epidemiologists who, without agreed definitions of what constitutes a case, find it difficult to describe patterns of occurrence of disease. Perhaps it is not very surprising that information about the descriptive epidemiology of peripheral neuropathy derived from population based studies is scarce.

What data do exist suggest that peripheral neuropathy may be rather commoner than is usually thought. A recent study, carried out in two regions of Italy, estimated the frequency of chronic symmetric symptomatic polyneuropathy in people over the age of 55 years attending general practitioners' surgeries. Probable polyneuropathy was diagnosed if they answered positively to a screening questionnaire for neuropathic symptoms and showed signs compatible with peripheral neuropathy when examined by a neurologist.[1] Around 8% of people met these diagnostic criteria for polyneuropathy. The commonest condition associated with polyneuropathy was diabetes. This study was not population based; only people already attending their general practitioner were included—a group in whom chronic disease is likely to be overrepresented and who will therefore be at increased risk of neuropathy. Despite this caveat, the rate of polyneuropathy detected was surprisingly high. Two studies of prevalence, one in Bombay[2] and the other in Sicily,[3] also suggest that peripheral neuropathy is common in the community. Cases were identified by a door to door survey. Those who answered positively to questions about sensory or motor symptoms were examined by a neurologist. In Bombay the prevalence of peripheral neuropathy was 2·4% and the commonest diagnoses were carpal tunnel syndrome and diabetic peripheral neuropathy. In Sicily, 7% of the population responded positively to the initial screening questions. After further investigation, diabetic neuropathy was diagnosed in 0·3% but no details about the frequency of other types of neuropathy were published.

Peripheral neuropathies are a disparate group of diseases. Attempts to consider them as a whole emphasise their contribution to the burden of disease and disability in the community, but may obscure interesting epidemiological features that could lead to a better understanding of aetiology. In this review we consider the commoner forms of peripheral neuropathy separately.

Diabetic neuropathies

The neuropathic complications of diabetes mellitus include distal, symmetric, predominantly sensory neuropathy, autonomic neuropathy, asymmetric proximal neuropathy, and cranial and other mononeuropathies. Several of these neuropathic manifestations may coexist in same patient. Although the time course and prognosis of the different types of neuropathy vary, little is known about how this reflects differences in underlying pathology.

An early study of diabetic peripheral neuropathy in a population used retrospective review of case records to ascertain symptoms or signs of neuropathy.[4] Four per cent of diabetic patients developed peripheral neuropathy within five years of diagnosis. By 20 years after diagnosis, the prevalence had risen to 15%. Distal symmetric sensory neuropathy predominated. Many surveys since, both population based and of clinical case series, have shown that these rates are probably underestimates. Using a case definition that required at least two of the following three criteria—sensory symptoms in hands or feet, sensory or motor signs on examination, or absent or diminished tendon reflexes—a large registry based study of insulin dependent diabetic patients found an overall prevalence of distal symmetric polyneuropathy of 34%, which rose to 58% in people 30 years of age and older.[5] A study of non-insulin dependent diabetic patients, using criteria in which decreased or absent thermal sensation replaced sensory or motor signs, reported a prevalence of 26%.[6]

A recently published investigation in which a cohort of incident cases of non-insulin dependent diabetes mellitus was followed up

MRC Environmental Epidemiology Unit, Southampton University, Southampton General Hospital, Southampton SO16 6YD, UK
C N Martyn

Department of Neurology, UMDS, Guys Hospital, London SE1 9RT, UK
R A C Hughes

Correspondence to:
Dr C N Martyn, MRC Environmental Epidemiology Unit, Southampton University, Southampton General Hospital, Southampton SO16 6YD, UK.

Table 1 Incidence of peripheral neuropathies

	Place	Incidence (per 100 000 person-years)	Reference
Bell's palsy	Minnesota, USA	25	83
	Texas, USA	23·5 men, 32·7 women	84
	Ehime, Japan	30	85
Cervical radiculopathy	Minnesota, USA	83	97
Guillain-Barré syndrome	Minnesota, USA	2·4 (1970–80)	27
	Farrara, Italy	2·7 (1991–3)	28
Carpal tunnel syndrome	Minnesota, USA	99	91
Neuralgic amyotrophy	Minnesota, USA	1·6	86

for 10 years found that 8% fulfilled criteria for definite or probable neuropathy at the time of diagnosis compared with 2% in the control group.[7] After 10 years of follow up, the prevalence of neuropathy had increased to 42% among diabetic patients and to 6% in controls. Electrophysiological investigations showed a more pronounced decrease in sensory and motor compound action potential amplitudes than in nerve conduction velocities in diabetic patients. This was interpreted as indicating that the underlying pathology was axonal degeneration rather than demyelination. Poor glycaemic control and low plasma concentrations of insulin independently of concentrations of glucose were associated with increased risk of development of neuropathy.

Lack of space prevents a detailed description of the many other studies that have been carried out but their findings are broadly similar. Poor glycaemic control and duration of diabetes have consistently been shown to be associated with neuropathy.[8] Other risk factors are age, height, male sex, and alcohol consumption although for these the evidence is less consistent. Systemic hypertension, cigarette smoking, and raised concentrations of plasma lipids are associated with increased risk of neuropathy in insulin dependent diabetes but not in non-insulin dependent diabetes. The central role of hyperglycaemia in the pathogenesis of diabetic peripheral neuropathy was confirmed in the large prospective Diabetes Control and Complications Trial. Intensive treatment of diabetes lowered the risk of developing clinical neuropathy by more than 60%.[9] Nerve conduction velocities were measured in over 1000 patients at entry to the trial and five years later. Significant differences were found between the intensive and conventional treatment groups. On average, the intensively treated group had faster sensory and motor conduction velocities and shorter F wave latencies than the conventionally treated group. Further, whereas most neurophysiological variables deteriorated over time among conventionally treated patients, they remained stable or showed modest improvement in the intensively treated group.[10]

Only one large population based study has investigated the prevalence of autonomic neuropathy in diabetes. Using three tests of autonomic function based on cardiovascular reflexes, the Oxford Community Diabetes Study found that nearly 17% of diabetic patients had at least one abnormal test.[11] Apart from erectile impotence, however, only 2·4% of the patients studied reported symptoms that could be attributed to autonomic dysfunction. Many other studies of clinic populations have also found that, whereas abnormal tests of autonomic function are common in diabetic patients, symptoms are relatively rare. There is some evidence to suggest that autonomic dysfunction in diabetes carries a poor prognosis. Mortality was high in two follow up studies of diabetic patients with abnormal tests of cardiovascular reflexes.[12,13] Autonomic neuropathy is a poor prognostic indicator in patients with advanced liver disease too.[14] This is an area that deserves further investigation.

Hereditary neuropathies

Charcot-Marie-Tooth disease is a heterogeneous group of disorders affecting the peripheral nerves and anterior horn cells of the spinal cord. Together they constitute the most commonly inherited form of peripheral neuropathy. Population surveys have been carried out which show large geographical variations in the frequency of the condition:[15–21] Libya 8 per 100 000 population; Nigeria 10 per 100 000; south Wales 17 per 100 000; northern Sweden 20 per 100 000; northern Spain 28 per 100 000; western Norway 41 per 100 000.

The most prevalent type is the demyelinating form, CMT1. In a study in northern Sweden, CMT1 accounted for 80% of cases whereas the axonal or neuronal form, CMT2, accounted for the remaining 20%.[19] A collaborative European study showed that about 70% of patients with CMT1 have an identifiable duplication of the gene for a 22 kDa peripheral nerve myelin protein PMP22 on the short arm of chromosome 17, at position 17p11·2.[22] In the others, various point mutations have been found in the PMP22, PO, and connexin 32 genes. The last is on the X chromosome and accounts for X linked cases. About 10% of families with autosomal dominant CMT1 have de novo duplications, usually, but not always, arising from duplication during male meiosis.[23] The severity of CMT is variable, even within families. Hereditary neuropathy may be subclinical, mild and late in onset, or severe from an early age. Hereditary neuropathy with liability to pressure palsies is an autosomal dominant condition, being due in most symptomatic cases (84% in the European collaborative study) to deletion of the same gene which is duplicated in the autosomal dominant subtype CMT1A at 17p11·2.[22] The phenotype is even more variable than in CMT1 and some cases are asymptomatic.

Amyloid neuropathy is the other common cause of hereditary neuropathy, being due to deposition of transthyretin, or less commonly other proteins, in the peripheral nerves, although it may also be an acquired disorder secondary to B cell dyscrasia and immunoglobulin light chain deposition. The nature of the mutation in the transthyretin gene determines the pattern of deposition and the presenting features of the neuropathy. The commonest mutation causes the substitution of methionine for valine at position 30 which results in a late onset, progressive, painful,

Table 2 Prevalence of peripheral neuropathies

		Prevalence (per 100 000 population)	Reference No
Overall	Italy	8000 (in people ≥ 55 y)	1
	Bombay, India	2400	2
Diabetic	Sicily	300	3
Carpal tunnel syndrome	Netherlands	5800 women, 600 men	90
Charcot-Marie-Tooth	Libya	8	15–21
	Nigeria	10	
	South Wales	17	
	Northern Sweden	20	
	Northern Spain	28	
	Western Norway	41	
Leprosy	South East Asia	116	65
	Africa	53	
	Central and South America	46	

predominantly sensory neuropathy, formerly called the Portuguese type or familial amyloid neuropathy type 1. It has been described from many different countries, including Portugal, Japan, Italy, Spain, Greece, and Sweden. There are few data on prevalence but published studies suggest that clusters of high prevalence occur in some areas. In northern Sweden the gene prevalence is 1500 per 100 000 but the disease is so mild and late in onset—or the penetrance so low—that the prevalence of symptomatic disease is only 31 per 100 000.[24] Studies of transthyretin intron polymorphisms have shown that there are multiple haplotypes, refuting the proposition that the disease had a single founder and was then spread round the world by Portuguese sailors.[25]

Neuropathy from infectious and inflammatory causes

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) has been the subject of over 30 population studies during the past 50 years, most of which have shown an annual incidence in the range 1·0 to 2·0 per 100 000 population. The condition seems to be reasonably evenly distributed throughout the world and incidence rates are probably fairly stable over time.[26] The annual incidence seemed to rise from 1·2 per 100 000 in 1953–6 to 2·7 per 100 000 in 1970–80 in Olmsted county, Rochester, USA.[27] Similarly the annual incidence rose from about 1·3 per 100 000 in the triennium 1981–3 to 2·7 per 100 000 in 1991–3 when surveyed in Ferrara, northern Italy.[28] These apparent increases in incidence were based on few cases and may be explained by increasing awareness and ascertainment of the disease.[28]

Whereas the incidence of GBS is low (but not very low, being about half that of multiple sclerosis), the cumulative effect of permanent disability produced in young people represents an important, but unrecognised public health problem. Thirteen per cent of 79 patients in a recent population based survey in south east England were left requiring aid to walk after a year, a disability likely to be permanent.[29]

The heterogeneity of GBS and lack of a gold standard diagnostic test bedevil useful aetiological deductions from population based surveys of the disease. In practice, the clinical picture is sufficiently striking that the diagnosis can be readily recognised in a community with ready access to neurological services and most cases conform to the accepted diagnostic criteria.[30] Unfortunately this clinical description embraces a heterogeneous group of pathological entities, of which at least 90% are thought to be acute inflammatory demyelinating polyradiculoneuropathy and the remainder are acute motor, or motor and sensory, axonal neuropathy.[31] None of the population based studies has been sufficiently complex to distinguish the different subtypes of GBS.

The disease occurs from infancy to extreme old age. There is a more or less linear increase in incidence with advancing years which would be compatible with lessening of immune suppressor mechanisms in old age and consequent increased susceptibility to autoimmune disease. In the largest series, collected in an active surveillance programme in the United States from 1979 to 1981, there was a small peak in the age distribution for young adults, especially women.[32] This might be explained by exposure to infections which are more common in that age group, which include *Campylobacter jejuni* and cytomegalovirus.

Males are more commonly affected than females in a ratio of 1·25 to 1.[33] Such male predominance is unusual for an autoimmune disease, but also occurs in Goodpasture's syndrome, which is due to autoantibodies against glomerular basement membrane. It is not clear whether this male predominant sex ratio is confined to the premenopausal age and explicable by a protective effect of oestrogen or to an X or Y chromosome gene. Such effects might operate at the level of susceptibility to an infection or control of an autoimmune response. The effect of sex on both factors has been shown in relevant experimental models. For instance, female mice experimentally infected with vesicular stomatitis virus developed less CNS virus load and recovered more quickly than males: the recovery was associated with an earlier, more vigorous inflammatory response.[34]

The occurrence of GBS is sporadic although rare, small epidemics have been reported.[35] For instance, an outbreak of nearly 4000 cases of gastroenteritis in a town in Jordan, attributed to *Shigella* contamination of the water, resulted in 19 cases of GBS, representing about four cases per 1000 reported cases of shigellosis.[36] There is no consistent seasonal pattern of incidence except in north China where there is a large increase in incidence of GBS in the summer months. This summer epidemic is due to an increase in incidence of acute motor axonal neuropathy in children and young adults.[37] Such a pattern strongly suggests exposure to a seasonal infection in the pathogenesis of this type of GBS in that region. The most likely candidate is *Campylobacter jejuni* enteritis: 66% of 38 cases had serological evidence of recent infection compared with 16% of village controls.[38]

Campylobacter jejuni is also the commonest identified infection preceding sporadic GBS in other countries. In large series of cases of GBS (n > 100) in the United Kingdom,[31 39] The Netherlands,[40] and the United States,[41] the frequency of serological evidence of recent *Campylobacter* infection has ranged from 26 to 36% of cases of GBS, far exceeding the incidence in control groups,[31 39] and making *Campylobacter* the commonest recognised antecedent infection. The favoured hypothesis is that *Campylobacter* lipopolysaccharide glycoconjugates share epitopes with axonal or Schwann cell glycolipids, stimulate autoimmune responses, and generate corresponding axonal or demyelinating autoimmune neuropathy. In particular the Gal(β1–3) GalNAc epitope is shared by the lipopolysaccharide in the walls of some *Campylobacter* strains and by ganglioside GM1 in axon membranes.[42 43] Although the general hypothesis that *Campylobacter* infections stimulate immune responses to cross reactive glyconjugates may still be correct, ganglioside GM1-like epitopes are not invariably present in the lipopolysaccharide prepared from *Campylobacter* isolated from the stools of patients with GBS.[44] There is a single report, needing confirmation, of induction of acute axonal neuropathy in chickens which had been fed or injected with *Campylobacter* isolated from the stool of a Chinese patient with the acute motor axonal neuropathy form of GBS.[45]

There have been many single reports, and also small series of cases of GBS after therapeutic injection of ganglioside preparations.[46–48] Many, but not all, of the affected patients have had antibodies to ganglioside GM1 in their serum. There was no rise in the incidence of GBS after the introduction of ganglioside treatment during ongoing epidemiological surveys of GBS in Italy. Case-control studies have not proved a causal connection but the circumstantial evidence is strong.[49]

GBS is such a striking illness that when it occurs after an event such as an immunisation, it tends to be reported either in the medical literature or in the law courts. With the exception of vaccinia, the old fashioned rabies vaccines, which contained myelin components,[50] and the 1976 United States swine influenza vaccine,[51] the evidence that immunisations trigger GBS is not strong. However, disproving small increases in risk is difficult in diseases as uncommon as GBS. In two case control studies, comprising over 200 cases in south east England, the odds ratio of cases having been immunised was 1·8, not significantly increased compared with controls, but the 95% confidence intervals ranged from 0·7 to 4·4.[52] The epidemiologically demonstrated association between swine influenza vaccine and GBS was never explained. Ongoing investigations of the association with *Campylobacter* have already contributed to the description of the acute axonal motor and motor and sensory subtypes of GBS and may well yield the secret of how a bacterial infection can give rise to an autoimmune reaction directed against axonal or Schwann cell derived antigens.

Large series, population studies, and large controlled trials have consistently shown the following to be adverse prognostic factors: old age, preceding gastrointestinal infection, serological or stool culture evidence of *Campylobacter* infection, severe acute illness (requirement for ventilation or severe upper limb weakness), electrophysiological evidence of axonal degeneration (small distally evoked muscle action potentials), and absence of treatment with plasma exchange or intravenous immunoglobulin.[31 40 53 54]

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

By contrast with GBS there is very little epidemiological information concerning CIDP (defined as an acquired idiopathic demyelinating neuropathy with a progressive phase > eight weeks). The distinction between the acute inflammatory demyelinating polyradiculoneuropathy form of GBS and CIDP may be artificial as the distribution of onset phases is unimodal, not bimodal,[55] and intermediate subacute forms occur.[56] It is probably an uncommon condition but the neurophysiological and nerve biopsy assessments required for its diagnosis are complex so that it is probably underdiagnosed. There are no reliable population estimates of its prevalence yet, but our own data suggest a minimum prevalence of at least 1 per 100 000. The only published information at present comes from large hospital series which suggest that the disease occurs throughout the world and at all ages. Its course is more often relapsing-remitting than progressive, and progressive cases tend to be older.[57] Antecedent infections are reported less commonly than before GBS, being recalled in only 25% of 40 patients in the most recent study in which this information was specifically sought.[58] Although immunisations have also been incriminated as triggering CIDP, the evidence that they either trigger CIDP or cause relapse is weak.[59]

HIV ASSOCIATED NEUROPATHY

Various peripheral nerve syndromes have been reported in association with HIV infection including acute and chronic inflammatory demyelinating neuropathies, distal sensory neuropathy—often of a painful type—and multiple mononeuropathy. In addition, treatment with dideoxynucleosides, particularly ddC, may cause a dose related toxic neuropathy.[60] Information about HIV associated neuropathy is mainly derived from case reports and follow up, often incomplete, of clinic based case series. The reported frequency of occurrence of peripheral neuropathy varies considerably, which probably reflects differences in duration of infection among cases in the different series.

A distal, symmetric, painful, predominantly sensory axonal neuropathy is the commonest peripheral nerve syndrome associated with HIV infection.[61] Two large studies have shown that it is rare in the early stages of infection. In a cohort of around 800 HIV positive airforce

personnel, all of whom had recently been considered fit for active duty, only 12 had symptoms or signs of neuropathy.[62] This finding confirmed the results of the multicentre AIDS cohort study.[63] Studies of groups of patients with more advanced disease have found higher rates.[60] Among 54 HIV infected patients referred to a neurological clinic over a 15 month period, distal symmetric peripheral neuropathies were present in 38. Two thirds of these had a distinct clinical syndrome characterised by painful paraesthesiae or sensations of burning in both feet and, in the eight patients who underwent sural nerve biopsy, axonal atrophy. There was a clear temporal relation between the onset of symptoms and cytomegalovirus infection. Neuropathies in the other patients were more heterogenous. They included multiple mononeuropathy, isolated mononeuropathies, and lumbosacral polyradiculopathy.

Demyelinating inflammatory polyneuropathy has been reported to occur at the time of seroconversion but it seems to be a rare event and is usually followed by complete recovery.[64]

LEPROSY

In global terms leprosy remains an important cause of peripheral neuropathy. Fortunately, multidrug treatment and World Health Organisation surveillance programmes are having a major impact. Between 1990 and 1994 there was a 55% fall in the worldwide prevalence although part of the decrease may be due to changes in case definition. The highest prevalence of leprosy is in South East Asia (116 per 100 000) compared with 53 per 100 000 in Africa and 46 per 100 000 in Central and South America.[65] In Europe and North America the disease is only seen in immigrants.

PARAPROTEINAEMIC NEUROPATHY

Serum monoclonal paraproteins were found in 10% of patients with otherwise unexplained peripheral neuropathy,[66] 10 times more often than expected in a population of elderly people. The associated paraproteins belonged to the IgM class in 60% of cases of neuropathy in two large series,[67 68] whereas in studies of serum paraproteins not associated with neuropathy, the IgG class accounted for 61% and IgM for only 8%.[69] The associated paraprotein is usually classified as being due to a monoclonal gammopathy of undetermined importance. This periphrasis implies absence of current malignancy but a potential for malignant transformation which requires follow up. Recognition of the association between the IgM paraprotein and demyelinating neuropathy led directly to the discovery of complement fixing antibodies directed against carbohydrate epitopes shared by myelin associated glycoprotein and a previously undiscovered peripheral nerve myelin glycolipid, sulphate-3-glucuronyl paragloboside. Transfer of the serum from patients with these antibodies has induced experimental demyelinating neuropathy in animals and there are anecdotal reports of improvement after treatment with plasma exchange and immunosuppression.[70] The antigenic target of the antibody action of other paraproteins are gradually being defined including IgM antibodies directed against ganglioside GM1 in multifocal motor neuropathy,[71] and IgM antibodies directed against disialosyl groups present on ganglioside GD3, GD1b, GT1b, and GQ1b in chronic large fibre sensory neuropathy.[72] The discovery of these autoantibodies in paraproteinaemic neuropathy has led to a search, which has sometimes been rewarding, for similar antibodies in peripheral neuropathy in which there is no paraprotein association. It is likely that other antibody specificities remain to be discovered. However, there are also other explanations for the association between a paraprotein and neuropathy including amyloid, vasculitis, and coincidence. Peripheral neuropathy is sometimes a feature of multiple myeloma, and is often present in the rarer caes of solitary myeloma.

Paraneoplastic neuropathy

Few studies have directly investigated how commonly neoplasms cause peripheral neuropathy. Lin *et al*[73] found that 2·3% of 520 cases of peripheral neuropathy attending neurological centres in Taiwan were due to neoplasm. Conversely between 2·5 and 5·5% of patients with lung or breast cancer have clinical evidence of a peripheral neuropathy.[74] Focal or multifocal radiculopathies, plexopathies, and neuropathies are usually due to infiltration or compression by the tumour. When symmetric polyneuropathies or neuronopathies are associated with a tumour, they are usually paraneoplastic manifestations. Paraneoplastic sensorimotor neuropathies are the most frequent syndrome, and are due to a wide variety of tumours, but especially carcinoma of the lung. Subacute sensory neuronopathy is a rather characteristic paraneoplastic syndrome, as about 20% of such cases do have an underlying carcinoma, which is usually a small cell lung carcinoma. In most cases investigation has disclosed the presence of antineuronal antibodies reacting with a family of nucleoproteins termed Hu, which strongly suggest an autoimmune pathogenesis.[75]

Toxic neuropathies

The peripheral nervous system is vulnerable to many toxic agents. In the past, heavy metals, especially lead, arsenic, and thallium, accounted for many cases of neuropathy. Occupational exposure to solvents such as n-hexane, carbon disulphide, and methyl-n-butyl ketone was previously a cause of peripheral sensorimotor neuropathy but now, in the western world at least, industrial legislation has resulted in strict control of permitted concentrations of these solvents in the workplace. Occasional outbreaks of neuropathy caused by industrial exposure are reported in economically developing countries. The epidemic of Jamaica ginger paralysis that occurred in the United States in 1930 and 1931 was due to

the contamination of illicit alcohol with tri-*o*-cresyl phosphate. The story is an interesting one—not least because of the scale of the outbreak. It is estimated that 50 000 people were affected.[76] Other sudden outbreaks of peripheral neuropathy due to tri-*o*-cresyl phosphate have been reported in India, South Africa, and Morocco.[77–79]

More recently, an epidemic of a neurological syndrome the clinical features of which were dominated by a peripheral sensorimotor neuropathy occurred in Spain as a result of the use of denatured rape seed oil that was sold as cooking oil. Neuropathological studies showed the unusual appearance of an intense inflammatory perineuritis followed by perineurial fibrosis with degeneration of myelinated axons. The oil contained high concentrations of peroxides and it was conjectured that nerve damage was caused by the action of free radicals.[80]

Alcohol

Peripheral nerve dysfunction is common in people who chronically misuse alcohol. There has been a long debate about whether this is due to a direct toxic effect of alcohol or whether it is a result of chronic nutritional deficiency. In a recent series of 107 alcoholic patients presenting at a Spanish hospital clinic, about a quarter showed abnormalities on tests of cardiovascular autonomic reflexes and a third fulfilled electrophysiological criteria of peripheral neuropathy.[81] Correlations between total lifetime dose of alcohol and sensory nerve compound action potential amplitudes were found but there was no relation to age, nutritional status, or the presence of other alcohol related diseases. Although thiamine deficiency has traditionally been thought to play a part in the pathogenesis of alcoholic neuropathy, a recent study of blood concentrations of free thiamine in chronic alcoholics showed no differences between those with and without peripheral neuropathy or between alcoholics and a control group.[82]

Bell's palsy

Bell's palsy, a unilateral, lower motor neuron facial paralysis, is the commonest condition affecting the facial nerve. Studies of incidence have been carried out in the United States and in Japan.[83–85] All relied on retrospective examination of hospital and clinic records to ascertain cases and are likely to have underestimated the frequency of mild cases that remained undiagnosed or were treated in primary care. Crude incidence rates in these studies were fairly similar: in Rochester, Minnesota, USA, annual incidence was 25 per 100 000 population; in Laredo, Texas, USA, 23·5 per 100 000 in men and 32·7 per 100 000 in women; and in Ehime prefecture, Japan, 30 per 100 000 population. Rates for men and women were similar in Rochester and in the Ehime prefecture. Logistic regression analysis of the data from Rochester suggested that complete facial weakness, pain other than in or around the ear, and systemic hypertension were the most important predictors of incomplete recovery but out of 206 patients only 28 (14%) experienced incomplete recovery.

Evidence implicating local reactivation of herpes simplex virus type 1 in the aetiology of Bell's palsy comes from a recent report of a small series of patients who had decompressive surgery of the facial nerve.[86] Fragments of DNA specific for herpes simplex virus were detected by Southern blot analysis in endoneurial fluid from the affected facial nerve or in tissue from biopsy of the posterior auricular muscle after amplification by polymerase chain reaction in 11 out of 14 patients. No such fragments were found in fluid or tissue from the control group which consisted of nine patients with Ramsay-Hunt syndrome and 12 patients with a mixture of other diagnoses.

Neuralgic amyotrophy

A population based study of neuralgic amyotrophy in Rochester, Minnesota identified 11 cases over a period of 12 years giving an overall annual incidence of 1·6 per 100 000 population.[87] Retrospective analysis of case series and case reports have suggested various antecedent events: various infectious illnesses, immunisations, surgery, intravenous drug misuse, intravenous administration of radiological contrast medium, trauma in areas of the body remote from the brachial plexus, and childbirth. Detailed electrophysiological investigation of a small case series showed various lesions of individual peripheral nerves or their branches sometimes occurring singly and sometimes in combination.[88] These authors hypothesised that the course of these nerves, especially their location across joints, selectively exposed them to mild focal trauma and rendered them more susceptible to the disease.

Some cases of neuralgic amyotrophy are familial. The condition is apparently inherited as an autosomal dominant trait and may be associated with mildly dysmorphic facial features. In linkage studies of two large pedigrees, the gene was mapped to the distal part of the long arm of chromosome 17.[89] However, the disorder is genetically, as well as clinically, distinct from mutation in the PMP22 gene associated with hereditary neuropathy with liability to pressure palsies.[90]

Carpal tunnel syndrome

Carpal tunnel syndrome, caused by compression of the median nerve where it passes under the transverse carpal ligament in the wrist, is a common diagnosis in neurology and rheumatology outpatient clinics but there is remarkably little information about the frequency of its occurrence in the population generally. In a population based study of its prevalence in The Netherlands, carpal tunnel syndrome had been previously diagnosed in 3·4% of women and was present, undiagnosed, in a further 5·8%.[91] By contrast, in men the overall preva-

lence was only 0·6%. The medical records linkage system at the Mayo clinic has been used to study the incidence of the condition. The crude annual incidence rate during the period 1961 to 1980 was 99 per 100 000. Age adjusted sex specific rates showed a female to male ratio of 3:1.[92] Incidence rates increased during each sequential five year period of the study, from 88 per 100 000 to 125 per 100 000 but it was thought that this increase was more likely to reflect better recognition of the condition than a true increase in the underlying incidence. Rates increased with age in men, but in women incidence peaked in the 45 to 54 age group.

Many risk factors for carpal tunnel syndrome have been identified. Associations with diabetes, hypothyroidism, rheumatoid arthritis, amyloidosis, pregnancy, and haemodialysis have been found in retrospective studies of clinic based case series. Most cases associated with pregnancy resolve spontaneously after delivery.[93] Case-control studies have added other risk factors to the list including a history of gynaecological surgery, particularly hysterectomy and oophorectomy,[94] recent weight gain, and use of oestrogen replacement therapy.[95] Several studies have confirmed carpal tunnel syndrome as an occupational disease. Repetitive movements of the wrist, especially if they involve flexion or strong force, and the use of vibrating hand tools, are associated with a greatly increased risk. The economic consequences may not have been sufficiently recognised. Although follow up of case series suggests that treatment of carpal tunnel syndrome by surgical decompression is moderately effective in relieving pain, a study in the United States of 191 men and women of working age treated surgically found that the mean time lost from work was four months and that 8% of cases lost more than one year from work.[96]

In a large cohort of women followed up in the Oxford Family Planning Association contraceptive study, carpal tunnel syndrome was associated with obesity and a history of menstrual disorders. There was also a strong and unexpected association with smoking. Standardised first referral rates for carpal tunnel syndrome tripled as smoking increased from 0 to 25 or more cigarettes per day.[97]

Cervical radiculopathy

Cervical radiculopathy is another disorder of the peripheral nervous system that is common in clinical neurological practice but which has hardly been studied epidemiologically. The best information again comes from the Mayo clinic's medical record linkage system. Between 1976 and 1990, 561 patients from the population of Rochester and Olmsted county were diagnosed as having cervical radiculopathy. The overall annual incidence was 83 per 100 000 and rates were higher in men than in women.[98] Incidence was highest in the age group 50 to 54 years. The C6 or C7 nerve roots were affected in 64% of cases. Although recurrence of symptoms was common—32% of patients reported recurrence during a median time of follow up of five years—90% had few or no symptoms at their last follow up. Although population based, case finding in this study depended on medical records and it is almost certain that mild cases of the condition were underrepresented.

Conclusions

Except in the areas of diabetic neuropathy and Guillain-Barré syndrome, there have been disappointingly few sound epidemiological investigations of peripheral neuropathies. As a result, we know little about variations in the geographical distribution of even the common forms of neuropathy and almost nothing about trends in their incidence over time. There seem to be many opportunities for useful collaboration between neurologists and epidemiologists both in extending our knowledge of the descriptive epidemiology of peripheral neuropathies and in investigating aetiology. The methodology of case-control studies has been used successfully in identifying some of the antecedent infections associated with Guillain-Barré syndrome but has been underemployed in the investigation of other peripheral neuropathies. Although there have been large advances in understanding the genetics of hereditary neuropathies, the enormous variability of phenotypic expression of many of these mutations remains a puzzle. It has been suggested that interactions with environmental factors or between the gene and other genes may be important. If the first is correct, an epidemiological approach has the potential to increase our knowledge of both aetiology and pathogenesis.

1 Beghi E, Monticelli ML, Amoruso L, *et al.* Chronic symmetrical polyneuropathy in the elderly—a field screening investigation in 2 Italian regions 1. Prevalence and general characteristics of the sample. *Neurology* 1995;**45**: 1832–6.

2 Bharucha NE, Bharucha AE, Bharucha EP. Prevalence of peripheral neuropathy in the Parsi community of Bombay. *Neurology* 1991;**41**:1315–7.

3 Savettieri G, Rocca WA, Salemi G, *et al.* Prevalence of diabetic neuropathy with somatic symptoms: a door-to-door survey in two Sicilian municipalities. *Neurology* 1993;**43**: 1115–20.

4 Palumbo PJ, Elvehack LR, Whisnant JP. Neurological complications of diabetes mellitus: transient ischaemic attack, stroke and peripheral neuropathy. In: Schoenberg BS, ed. *Neurological epidemiology: principles and clinical applications*. New York: Raven Press, 1978:593–601.

5 Maser RE, Steenkiste AR, Dorman JS, *et al.* Epidemiological correlates of diabetic neuropathy: report from Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes* 1989;**38**:1456–61.

6 Franklin GM, Kahn LB, Baxter J, Marshall JA, Hamman RF. Sensory neuropathy in non-insulin-dependent diabetes mellitus: the San Luis Valley Diabetes Study. *Am J Epidemiol* 1990;**131**:633–43.

7 Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995;**333**:89–94.

8 Orchard TJ, Dorman JS, Maser RE, *et al.* Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 1990;**39**:1116–24.

9 DCCT Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. *Ann Intern Med* 1995;**122**:561–8.

10 Albers JW, Kenny DJ, Brown M, *et al.* Effect of intensive diabetes treatment on nerve conduction in the diabetes control and complications trial. *Ann Neurol* 1995;**38**: 869–80.

11 Neil HA, Thompson AV, John S, McCarthy ST, Mann JI. Diabetic autonomic neuropathy: the prevalence of impaired heart rate variability in a geographically defined population. *Diabet Med* 1989;**6**:20–4.

12 Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med* 1980;**49**: 95–108.
13 Flynn MD, O'Brien IA, Corrall RJM. The prevalence of autonomic and peripheral neuropathy in insulin-treated diabetic subjects. *Diabet Med* 1995;**12**:310–3.
14 Fleckenstein JF, Frank SM, Thuluvath PJ. Presence of autonomic neuropathy is a poor prognostic indicator in patients with advanced liver disease. *Hepatology* 1996;**23**: 471–5.
15 Radhakrishnan K, El Mangoush MA, Gerryo SE. Descriptive epidemiology of selected neuromuscular disorders in Benghazi, Libya. *Acta Neurol Scand* 1987;**75**: 95–100.
16 Osuntokun BO, Adeuja AOG, Schoenberg BS, *et al.* Neurological disorders in Nigerian Africans: a community-based study. *Acta Neurol Scand* 1987;**75**:13–21.
17 MacMillan JC, Harper PS. The Charcot-Marie-Tooth syndrome: clinical aspects from a population study in South Wales, UK. *Clinical Genetics* 1994;**45**:128–34.
18 Hagberg B, Westerberg B. Hereditary motor and sensory neuropathies in Swedish children. I. Prevalence and distribution by disability groups. *Acta Paediatrica Scandinavica* 1983;**72**:379–83.
19 Holmberg BH. Charcot-Marie-Tooth disease in northern Sweden: an epidemiological and clinical study. *Acta Neurol Scand* 1993;**87**:416–22.
20 Combarros O, Calleja J, Polo JM, Berciano J. Prevalence of hereditary motor and sensory neuropathy in Cantabria. *Acta Neurol Scand* 1987;**75**:9–12.
21 Skre H. Genetic and clinical aspects of Charcot-Marie-Tooth disease. *Clin Genet* 1974;**6**:98–118.
22 Nelis E, van Broeckhoven C. Estimation of the mutation frequencies in Charcot-Marie-Tooth disease type 1 and hereditary neuropathy with liability to pressure palsies: a European collaborative study. *Eur J Hum Genet* 1996;**4**: 25–33.
23 Blair IP, Nash J, Gordon MJ, Nicholson GA. Prevalence and origin of de novo duplications in Charcot-Marie-Tooth disease type 1A: first report of a de novo duplication with a maternal origin. *Am J Hum Genet* 1996;**58**: 472–6.
24 Holmberg BH, Holmgren G, Nelis E, van Broeckhoven C, Westerberg B. Charcot-Marie-Tooth disease in northern Sweden: pedigree analysis and the presence of the duplication in chromosome 17p11·2. *J Med Genet* 1994;**31**: 435–41.
25 Reilly M, Staunton H. Peripheral nerve amyloidosis. *Brain Pathol* 1996;**6**:163–77.
26 Hughes RAC, Rees JH. Clinical and epidemiological features of Guillain-Barré syndrome. 1996 (in press).
27 Beghi E, Kurland LT, Mulder DW, Wiederholt WC. Guillain-Barré syndrome: clinicoepidemologic features and effect of influenza vaccine. *Arch Neurol* 1996;**42**: 1053–7.
28 Govoni V, Granieri E, Casetta I, *et al.* The incidence of Guillain-Barré syndrome in Ferrara, Italy: is the disease really increasing? *J Neurol Sci* 1996;**137**:62–8.
29 Rees JH, Thompson RD, Hughes RAC. An epidemiological study of Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry* 1996;**61**:215.
30 Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. *Ann Neurol* 1990;**27**(suppl):S21–4.
31 Rees JH, Soudain SE, Gregson NA, Hughes RAC. A prospective case control study to investigate the relationship between Campylobacter jejuni infection and Guillain-Barré syndrome. *N Engl J Med* 1995;**333**:1374–9.
32 Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barré syndrome in the United States, 1979–80 and 1980–1. Lack of an association with influenza vaccination. *JAMA* 1982;**248**:698–700.
33 Kaplan JE, Schonberger LB, Hurwitz ES, Katona P. Guillain-Barre syndrome in the United States 1978–81; additional observations from the national surveillance system. *Neurology* 1983;**33**:633–7.
34 Barna M, Komatsu T, Zhengbiao B, Reiss CS. Sex differences in susceptibility to viral infection of the central nervous system. *J Neuroimmunol* 1996;**67**:31–9.
35 Roman GC. Tropical neuropathies. In: Hartung H-P, ed. *Peripheral neuropathies: part 1.* London: Baillière Tindall 1995;469–87.
36 Khoury SA. Guillain-Barré syndrome: epidemiology of an outbreak. *Am J Epidemiol* 1978;**197**:433–8.
37 McKhann GM, Cornblath DR, Griffin JW, *et al.* Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. *Ann Neurol* 1993;**33**:333–42.
38 Ho TW, Mishu B, Li CY, *et al.* Guillain-Barré syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. *Brain* 1995; **118**:597–605.
39 Winer JB, Hughes RAC, Anderson MJ, Jones DM, Kangro H, Watkins RFP. A prospective study of acute idiopathic neuropathy. II. Antecedent events. *J Neurol Neurosurg Psychiatry* 1988;**51**:613–8.
40 Van der Meché FGA, Schmitz PIM, Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. *N Engl J Med* 1992;**326**:1123–9.
41 Mishu B, Ilyas A, Koski C, *et al.* Serologic evidence of previous Campylobacter jejuni infection in patients with Guillain-Barré syndrome. *Ann Intern Med* 1993;**118**: 947–53.
42 Aspinall GO, Fujimoto S, McDonald AG, Pang H, Kurjanczyk LA, Penner JL. Lipopolysaccharides from *Campylobacter jejuni* associated with Guillain-Barré syndrome patients mimic human gangliosides in structure. *Infect Immun* 1994;**62**:2122–5.
43 Yuki N, Taki T, Takahashi M, *et al.* Penner's serotype 4 of Campylobacter jejuni has a lipopolysaccharide that bears a GM1 ganglioside epitope as well as one that bears a GD1a epitope. *Infect Immun* 1994;**62**:2101–3.
44 Gregson NA, Rees JH, Hughes RAC. Patterns of reactivity between IgG antiGM1 ganglioside antibodies and the lipopolysaccharide fractions of Campylobacter jejuni isolates from patients with Guillain-Barré syndrome. *J Neuroimmunol* 1996 (in press).
45 Li C, Xue P, Tian W, Liu R, Yang C. Experimental Campylobacter jejuni infection in the chicken: an animal model of axonal Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry* 1996;**61**:279–84.
46 Illa I, Ortiz N, Gallard E, Juarez C, Grau JM, Dalakas MC. Acute axonal Guillain-Barré syndrome with IgG antibodies against motor axons following parenteral gangliosides. *Ann Neurol* 1995;**38**:218–24.
47 Landi G, D'Alessandro R, Dossi BC, Ricci SSi. Gangliosides and the Guillain-Barré syndrome. *BMJ* 1994;**308**:1638.
48 Landi G, D'Alessandro R, Dossi BC, Ricci S, Simone IL, Ciccone A. Guillain-Barré syndrome after exogenous gangliosides in Italy. *BMJ* 1993;**307**:1463–4.
49 Beghi E. Exposure to exogenous gangliosides and Guillain-Barré syndrome. *Neuroepidemiology* 1995;**14**:45–8.
50 Hughes RAC. *Guillain-Barré syndrome.* Heidelberg: Springer-Verlag, 1990.
51 Schonberger LB, Bregman DJ, Sullivan-Bolynai JZ, *et al.* Guillain-Barre syndrome following vaccination in the national influenza immunization program, United States 1976–7. *Am J Epidemiol* 1979;**110**:105–23.
52 Hughes RAC, Rees J, Smeeton N, Winer J. Vaccines and Guillain-Barré syndrome. *BMJ* 1996;**312**:1475–6.
53 Winer JB, Hughes RAC, Osmond C. A prospective study of acute idiopathic neuropathy. I. Clinical features and their prognostic value. *J Neurol Neurosurg Psychiatry* 1988;**51**:605–12.
54 McKhann GM, Griffin JW, Cornblath DR, *et al.* Plasmapheresis and Guillain-Barré syndrome: analysis of prognostic factors and the effect of plasmapheresis. *Ann Neurol* 1988;**23**:347–53.
55 Gibbels E, Giebisch U. Natural course of acute and chronic monophasic inflammatory demyelinating polyneuropathies (IDP). *Acta Neurol Scand* 1992;**85**:282–91.
56 Hughes R, Sanders E, Hall S, Atkinson P, Colchester A, Payan J. Subacute idiopathic demyelinating polyradiculoneuropathy. *Arch Neurol* 1992;**49**:612–6.
57 McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy. *Brain* 1987;**110**:1617–30.
58 Mélendez-Vásquez C, Redford J, Choudhary PP, *et al.* Immunological investigation of chronic inflammatory demyelinating polyradiculoneuropathy. *J Neuroimmunol* 1997 (in press).
59 Hughes RAC, Choudhary PP, Osborn M, Rees JH, Sanders EACM. Immunisation and risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve* 1996;**19**:1230–1.
60 Fichtenbaum CJ, Clifford DB, Powderly WG. Risk factors for dideonucleoside-induced toxic neuropathy in patients with the human immunodeficiency virus infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;**10**: 169–74.
61 Fuller GN, Jacobs JN, Guiloff RJ. Nature and incidence of peripheral nerve syndromes in HIV infection. *J Neurol Neurosurg Psychiatry* 1993;**56**:372–81.
62 Barohn RJ, Gronseth GS, LeForce BR, *et al.* Peripheral nervous system involvement in a large cohort of human immunodeficiency virus-infected individuals. *Arch Neurol* 1993;**50**:167–71.
63 McArthur JC, Cohen BA, Selnes OA, *et al.* Low prevalence of neurological and neuropsychological abnormalities in otherwise healthy HIV-1 infected individuals: results from the multicenter AIDS cohort study. *Ann Neurol* 1989;**26**:601–11.
64 Leger JM, Bouche P, Bolgert F, *et al.* The spectrum of polyneuropathies in patients infected with HIV. *J Neurol Neurosurg Psychiatry* 1989;**52**:1369–74.
65 World Health Organisation. Progress towards eliminating leprosy as a public health problem. *Wkl Epidemiol Rec* 1994;**20**:145–51.
66 Kelly JJ, Kyle RA, O'Brien PC, Dyck PJ. The prevalence of monoclonal gammopathy in peripheral neuropathy. *Neurology* 1981;**31**:1480–3.
67 Yeung KB, Thomas PK, King RHM, *et al.* The clinical spectrum of peripheral neuropathies associated with benign monoclonal IgM, IgG, and IgA paraproteinaemia. Comparative clinical, immunological, and nerve biopsy findings. *J Neurol* 1991;**238**:383–91.
68 Gosselin S, Kyle RA, Dyck PJ. Neuropathy associated with monoclonal gammopathies of undetermined significance. *Ann Neurol* 1991;**30**:54–61.
69 Axelsson U, Bachmann R, Hällén J. Frequency of pathological proteins (M components) in 6995 sera from an adult population. *Acta Med Scand* 1966;**179**:235–47.
70 Tatum AH. Experimental paraprotein neuropathy, demyelination by passive transfer of human IgM antimyelin-associated glycoprotein. *Ann Neurol* 1993;**33**: 502–6.

71 Nobile-Orazio E. Multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 1996;**60**:599–603.
72 Willison HJ, Paterson G, Veitch J, Inglis G, Barnett SC. Peripheral neuropathy associated with monoclonal IgM anti-Pr_2 cold agglutinins. *J Neurol Neurosurg Psychiatry* 1993;**56**:1178–83.
73 Lin KP, Kwan SY, Chen SY, *et al.* Generalized neuropathy in Taiwan: an etiologic survey. *Neuroepidemiology* 1993; **12**:257–61.
74 Croft PB, Wilkinson M. The incidence of carcinomatous neuromyopathy in patients with various types of carcinoma. *Brain* 1965;**88**:427–34.
75 Smitt PS, Posner JB. Paraneoplastic peripheral neuropathy. In: Hartung H-P, ed. *Peripheral neuropathies: part I.* London: Baillière Tindall, 1996:443–68.
76 Morgan JP, The Jamaica ginger paralysis. *JAMA* 1982; **248**:1864–7.
77 Vora DD, Dastur DK, Beatriz M, *et al.* Toxic polyneuropathies in Bombay due to ortho-cresyl phosphate poisoning. *J Neurol Neurosurg Psychiatry* 1962;**25**:234–42.
78 Susser M, Stein Z. An outbreak of tri-ortho-cresyl phosphate poisoning in Durban. *Br J Ind Med* 1957;**14**:111.
79 Smith HV Spalding JMK. Outbreak of paralysis in Morocco due to ortho-cresyl phosphate poisoning. *Lancet* 1959;**ii**:1019.
80 Ricoy JR, Cabello A, Rodriguez J, Tellez I. Neuropathological studies on the toxic syndrome related to adulterated rapeseed oil in Spain. *Brain* 1983;**106**: 817–35.
81 Monforte R, Estruch R, VallsSole J, Nicholas J, Urbano Marquez A. Autonomic and peripheral neuropathies in patients with chronic alcoholism: a dose-related toxic effect of alcohol. *Arch Neurol* 1995;**52**:45–51.
82 Poupon RE, Gervaise G, Riant P, Houin G, Tillement JP. Blood thiamine and thiamine phosphate concentrations in excessive drinkers with or without peripheral neuropathy. *Alcohol Alcohol* 1990;**25**:605–11.
83 Katusic SK, Beard CM, Wiederholt WC, *et al.* Incidence, clinical features, and prognosis in Bell's palsy, Rochester, Minnesota, 1968–82. *Ann Neurol* 1986;**20**:622–7.
84 Yanagihara N. Incidence of Bell's palsy. *Ann Otol Rhinol Laryngol* 1988;**97**:3–4.
85 Brandenburg NA, Annegers JF. Incidence and risk factors for Bell's palsy in Laredo, Texas: 1974–82 *Neuroepidemiology* 1993;**12**:313–25.
86 Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N. Bell's palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. *Ann Intern Med* 1996;**124**:27–30.
87 Beghi E, Kurland LT, Mulder DW, Nicolosi A. Brachial plexus neuropathy in the population of Rochester, Minnesota, 1970–81. *Ann Neurol* 1985;**18**:320–3.
88 England JD, Sumner AJ. Neuralgic amyotrophy: an increasingly diverse entity. *Muscle Nerve* 1987;**10**:60–8.
89 Pellegrino JE, Rebbeck TR, Brown MJ, Bird TD, Chance PF. Mapping of hereditary neuralgic amyotrophy (familial brachial plexus neuropathy) to distal chromosome 17q. *Neurology* 1996;**46**:1128–32.
90 Gouider R, LeGuern E, Emile J, *et al.* Hereditary neuralgic amyotrophy and hereditary neuropathy with liability to pressure palsies. *Neurology* 1994;**44**:2250–2.
91 DeKrom MC, Knipschild PG, Kester AD, Thijs CT, Boekkooi, PF, Spaans F. Carpal tunnel syndrome: prevalence in the general population. *J Clin Epidemiol* 1992; **45**:373–6.
92 Stevens JC, Sun S, Beard CM, O'Fallon WM, Kurland LT. Carpal tunnel syndrome in Rochester, Minnesota, 1961–80. *Neurology* 1988;**38**:134–8.
93 Ekman-Ordeberg G, Salgeback S, Ordeberg G. Carpal tunnel syndrome in pregnancy. A prospective study. *Acta Obstet Gynecol Scand* 1987;**66**:233–5.
94 Cannon LJ, Bernacki EJ, Walter SD. Personal and occupational factors associated with carpal tunnel syndrome. *J Occup Med* 1981;**23**:255–8.
95 Dieck GS, Kelsey JL. An epidemiologic study of the carpal tunnel syndrome in an adult female population. *Prev Med* 1985;**14**:63–9.
96 Adams ML, Franklin GM, Barnhart S. Outcome of carpal tunnel surgery in Washington State workers' compensation. *Am J Ind Med* 1994;**25**:527–36.
97 Vessey MP, Villard-Mackintosh L, Yeates D. Epidemiology of carpal tunnel syndrome in women of child-bearing age. Findings in a large cohort study. *Int J Epidemiol* 1990;**19**:43–7.
98 Radhakrishnan K, Litchy WJ, O'Fallon WM, Kurland LT. Epidemiology of cervical radiculopathy: a population based study from Rochester, Minnesota. *Brain* 1994; **117**:325–35.